9 Drug Metabolism

9.1 Introduction

Drug metabolism or biotransformations are the chemical reactions that are responsible for the conversion of drugs into other products (**metabolites**) within the body before and after they have reached their sites of action. It usually occurs by more than one route (Figure 9.1, R-(+)-warfarin). These routes normally consist of a series of enzyme controlled reactions. Their end products are normally pharmacologically inert compounds, which are more easily excreted than the original drug. The reactions involved in these routes are classified for convenience as **Phase I** (see section 9.4) and **Phase II** (see section 9.5) reactions. Phase I reactions either introduce or unmask functional groups, which are believed to act as a centre for Phase II reactions. The products of Phase I reactions are often more water soluble and so more readily excreted than the parent drug. Phase II reactions produce compounds that are often very water soluble and usually form the bulk of the inactive excreted products of drug metabolism.

The rate of drug metabolism controls the duration and intensity of the action of many drugs by controlling the amount of the drug reaching its target site. In addition, the metabolites produced may be pharmacologically active (see section 9.2). Consequently, it is important in the development of a new drug to document the behaviour of the metabolic products of a drug as well as that of their parent drug in the body. Furthermore, in the case of prodrugs, metabolism is also responsible for liberating the active form of the drug.

9.1.1 The stereochemistry of drug metabolism

The body contains a number of nonspecific enzymes that form part of its defence against unwanted xenobiotics. Drugs are metabolized by both these

Fundamentals of Medicinal Chemistry, Edited by Gareth Thomas

ISBN 0 470 84306 3 (Hbk), ISBN 0 470 84307 1 (pbk)

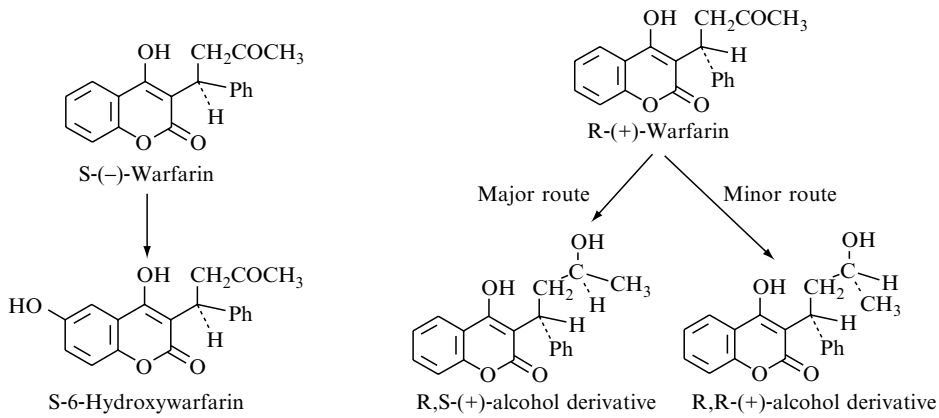
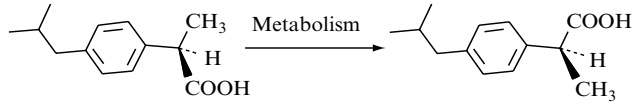


Figure 9.1 The different metabolic routes of S-(−)-warfarin and R-(+)-warfarin in humans

enzymes and the more specific enzymes that are found in the body. The latter enzymes usually catalyse the metabolism of drugs that have structures related to those of the normal substrates of the enzyme and so are to a certain extent stereospecific. The stereospecific nature of some enzymes means that enantiomers may be metabolized by different routes, in which case they could produce different metabolites (Figure 9.1).

In some cases an inert enantiomer is metabolized into its active enantiomer. For example, R-ibuprofen is inactive but is believed to be metabolized to the active analgesic S-ibuprofen.



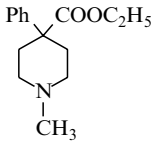
A direct consequence of the stereospecific nature of many metabolic processes is that racemic modifications must be treated as though they contained two different drugs, each with its own pharmacokinetic and pharmacodynamic properties. Investigation of these properties must include an investigation of the metabolites of each of the enantiomers of the drug. Furthermore, if a drug is going to be administered in the form of a racemic modification, the metabolism of the racemic modification must also be determined, since this could be different from that observed when the pure enantiomers are administered separately.

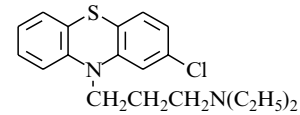
9.1.2 Biological factors affecting metabolism

The metabolic differences found within a species are believed to be due to variations in age, sex, genetics and diseases. In particular, diseases that affect the liver will have a large effect on drug metabolism. Diseases of organs, such as the kidneys and lungs, that are less important centres for metabolism will also affect the excretion of metabolic products. Consequently, when testing new drugs, it is essential to design trials to cover all these aspects of metabolism.

1. **Age**. The ability to metabolize drugs is lower in the very young (under 5) and the elderly (over 60). However, it is emphasized that the quoted ages are approximate and the actual changes will vary according to the individual and their lifestyle. In the foetus and the very young (neonates), many metabolic routes are not fully developed. This is because the enzymes equired by metabolic processes are not produced in sufficient quantities until several months after birth. Children (above 5) and teenagers usually have the same metabolic routes as adults. However, their smaller body volume means that smaller doses are required to achieve the desired therapeutic effect.

2. **Sex**. The metabolic pathway followed by a drug is normally the same for both males and females. However, some sex related differences in the metabolism of anxiolytics, hypnotics and a number of other drugs have been observed. Pregnant women will also exhibit changes in the rate of metabolism of some drugs. For example, the metabolism of both the analgesic pethidine and the antipsychotic chlorpromazine are reduced during pregnancy.

Pethidine 

Chlorpromazine 

3. **Genetic variations**. Variations in the genetic codes of individuals can result in the absence of enzymes, low concentrations of enzymes or the formation of enzymes with reduced activity. These differences in enzyme concentration and activity result in individuals exhibiting different metabolic rates and in some cases different pharmacological responses for the same drug. An individual's inability to metabolize a drug could result in that drug accumulating in the body. This could give rise to unwanted effects.

9.1.3 Environmental factors affecting metabolism

The metabolism of a drug is also affected by lifestyle. Poor diet, drinking, smoking and drug abuse may all have an influence on the rate of metabolism. The use of over-the-counter self-medicaments may also affect the rate of metabolism of an endogenous ligand or a prescribed drug. Since the use of over-the-counter medicaments is widespread, it can be difficult to assess the results of some large scale clinical trials.

9.1.4 Species and metabolism

Different species often respond differently to a drug. This is believed to be due to differences in metabolism between species. These metabolic differences may take the form of either different metabolic pathways for the same compound or different rates of metabolism when the pathway is the same. Both deviations are though to be largely due to enzyme deficiencies or sufficiencies.

9.2 Secondary pharmacological implications of metabolism

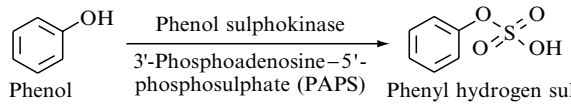
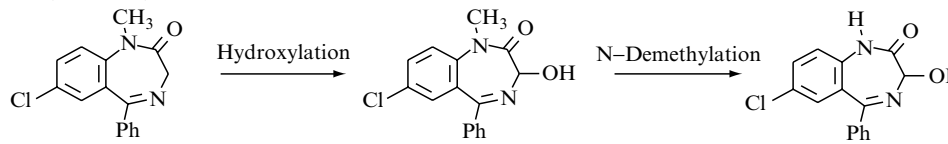
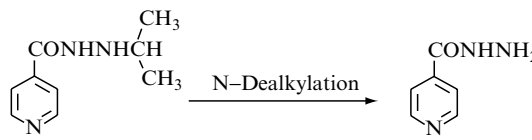
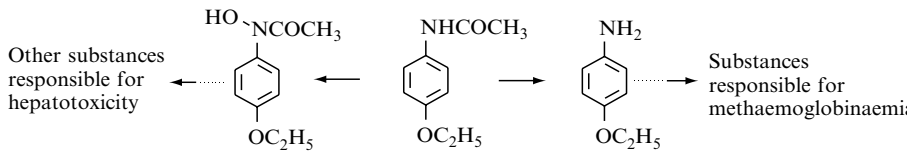
Metabolites may be either pharmacologically inactive or active. Active metabolites may exhibit a similar activity to the drug or a different activity or be toxic (Table 9.1). In addition, they may exhibit different side effects.

9.3 Sites of action

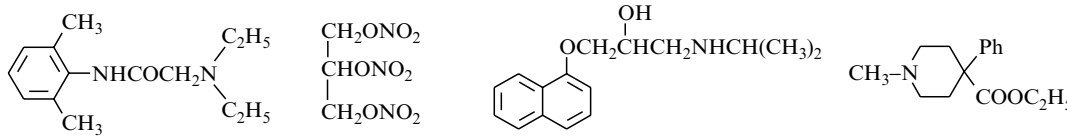
Drug metabolism can occur in all tissues and most biological fluids. However, the widest range of metabolic reactions occurs in the liver. A more substrate-selective range of metabolic processes takes place in the kidney, lungs, brain, placenta and other tissues.

Orally administered drugs may be metabolized as soon as they are ingested. However, the first region where a significant degree of drug metabolism occurs is usually in the GI tract and within the intestinal wall. Once absorbed from the GI tract, many potential and existing drugs are extensively metabolized by first pass metabolism (see section 8.5). For example, the first pass metabolism of

Table 9.1 Some of the types of secondary pharmaceutical activity of metabolites. Note that not all the possible metabolic routes for a drug are given in the examples

Metabolite activity	Example and notes
Inactive	Routes that result in the formation of inactive metabolites are often referred to as detoxification  Phenol → Phenyl hydrogen sulphate
Similar activity to the drug	The metabolite may exhibit either a different potency or duration of action or both to the original drug.  Diazepam (Sustained anxiolytic action) → Temazepam (short duration) → Oxazepam (Short duration)
Different activity	 Ipronazid (antidepressant) → Isoniazid (antituberculosis)
Toxic metabolites	 N-Hydroxy phenacetin (hepatotoxic) ← Phenacetin (analgesic) → Phenetidine (4-ethoxyaniline)

some drugs such as lignocaine is so complete that they cannot be administered orally. The bioavailability of other drugs, such as nitroglycerine (vasodilator), propranolol (antihypertensive) and pethidine (narcotic analgesic), is significantly reduced by their first pass metabolism.



Lignocaine — Nitroglycerine — Propranolol — Pethidine

9.4 Phase I metabolic reactions

The main Phase I reactions are biological oxidations, reductions, hydrolyses, hydrations, deacetylations and isomerizations, although a wide range of other reactions are included in this category. A knowledge of these biological reactions and the structure of a molecule makes it possible to predict its most likely metabolic products. However, the complex nature of biological systems makes an accurate comprehensive prediction difficult. As a result, the identification of the metabolites of a drug and their significance is normally determined by experiment during its preclinical and Phase I trials. Prediction of the possible products can be of some help in these identifications, although it should not be allowed to obscure the possible existence of unpredicted metabolites. Furthermore, computer based prediction systems are becoming available but lack sufficient data to fully predict the metabolic route of a specific compound from its structure.

9.4.1 Oxidation

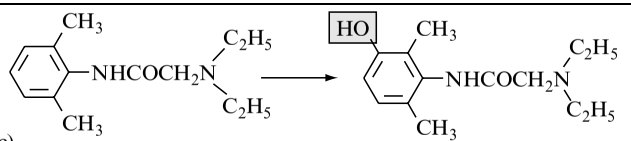
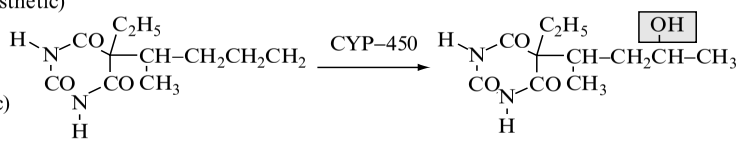
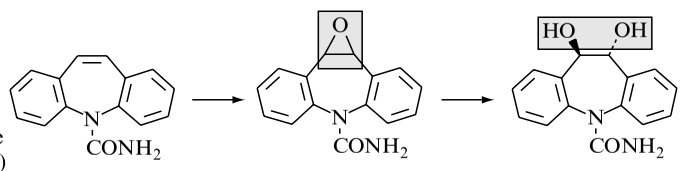
Oxidation is by far the most important Phase I metabolic reaction. One of the main enzyme systems involved in the oxidation of xenobiotics appears to be the so called **mixed function oxidases** or **monooxygenases**, which are found mainly in the smooth endoplasmic reticulum of the liver but also occur, to a lesser extent, in other tissues. These enzymes tend to be nonspecific, catalysing the metabolism of a wide variety of compounds (Table 9.2). Two common mixed function oxidase systems are the cytochrome P-450 (CYP-450) and the flavin monoxygenase (FMO) systems (Appendix 12). The overall oxidations of these systems take place in a series of oxidative and reductive steps, each step being catalysed by a specific enzyme. Many of these steps require the presence of molecular oxygen and either NADH or NADPH as co-enzymes.

A number of other enzymes, such as monoamine oxidase, alcohol dehydrogenase and xanthine oxidase, are also involved in drug metabolism. These enzymes tend to be more specific, oxidizing xenobiotics related to the normal substrate for the enzyme.

9.4.2 Reduction

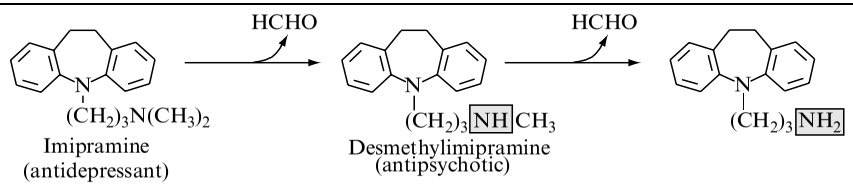
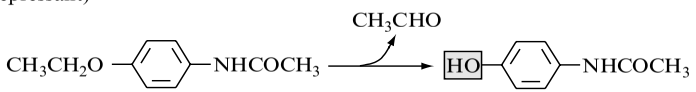
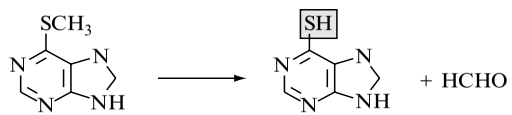
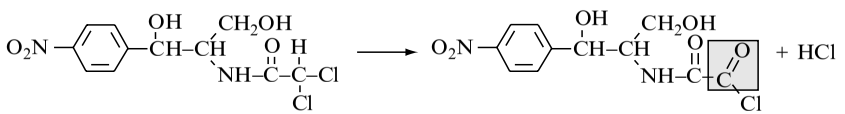
Reduction is an important reaction for the metabolism of compounds that contain reducible groups, such as aldehydes, ketones, alkenes, nitro groups,

Table 9.2 Examples of mixed function oxidase catalysed oxidations. Oxidation introduces or reveals new functional groups (shaded). Note: these reactions are not the only routes for the metabolism of the drugs used as examples

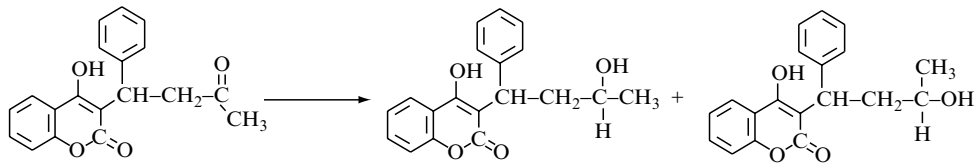
Type of reaction (groups)	Example
Aromatic hydroxylation (aromatic C–H)	 Lignocaine (local anaesthetic)
Aliphatic hydroxylation (aliphatic C–H)	 Pentobarbitone (sedative, hypnotic)
Epoxidization (aromatic and alkene groups)	 Carbamazepine (anticonvulsant)

(*continues overleaf*)

Table 9.2 *(continued)*

Type of reaction (groups)	Example
Dealkylation (methyl and ethyl secondary amines, tertiary amines, tertiary amines, ethers and thioethers. The methanal and ethanal produced are often excreted via the lungs, giving the patient bad breath.)	 Imipramine (antidepressant) Desmethylimipramine (antipsychotic)  Phenacetin (analgesic) Paracetamol (analgesic)  6–Methylthiopurine 6–Mercaptopurine (anticancer)
Oxidative dehalogenation The reactive electrophilic acyl and carbonyl compounds produced by oxidative dehalogenation may react with nucleophilic biological molecules such as DNA, proteins, lipids and carbohydrates to possibly form toxic metabolites.	 Chloramphenicol (antibiotic) Highly reactive xamyl chloride derivative

azo groups and sulphoxides. The enzymes used to catalyse metabolic reductions are usually specific in their action. Many of them require NADPH as a coenzyme. Reduction of some functional groups results in the formation of stereoisomers. Although this means that two metabolic routes may be necessary to deal with the products of the reduction, only one product usually predominates. For example, R(+)-warfarin is reduced to a mixture of the corresponding RS(+) and RR(+) diastereoisomers, the RS(+) isomer being the major product.



9.4.3 Hydrolysis

Hydrolysis is an important metabolic reaction for drugs whose structures contain ester and amide groups. All types of ester and amide can be metabolized by this route. Ester hydrolysis is often catalysed by specific esterases in the liver, kidney and other tissues as well as non-specific esterases such as acetylcholinesterases and pseudocholinesterases in the plasma. Amide hydrolysis is also catalysed by non-specific esterases in the plasma as well as amidases in the liver. More specific enzyme systems are able to hydrolyse sulphate and glucuronate conjugates as well as hydrate epoxides, glycosides and other moieties.

The hydrolysis of esters is usually rapid whilst that of amides if often much slower. This makes esters suitable as prodrugs (see Section 9.8) and amides a potential source for slow release drugs.

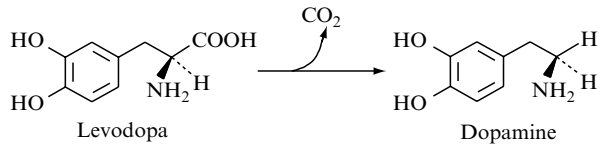
9.4.4 Hydration

Hydration, in the context of metabolism, is the addition of water to a structure. Epoxides are readily hydrated to diols (see carbamazepine, Table 9.1), the reaction being catalysed by the enzyme epoxide hydrolase.

9.4.5 Other Phase I reactions

The reactions involved in Phase I metabolism are not limited to those discussed in the previous sections. In theory, any suitable organic reaction could be

utilized in a metabolic route. For example, the initial stage in the metabolism of L-dopa is decarboxylation.



Levodopa Dopamine

9.5 Phase II metabolic routes

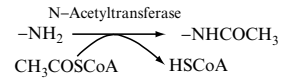
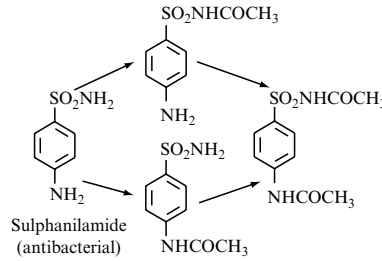
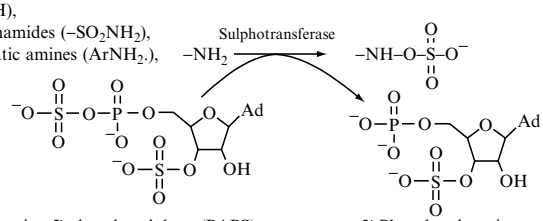
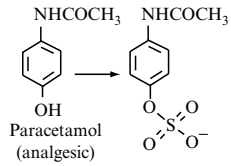
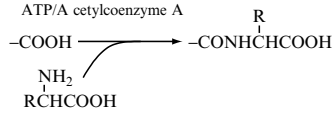
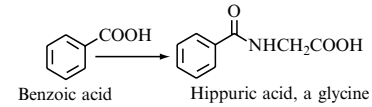
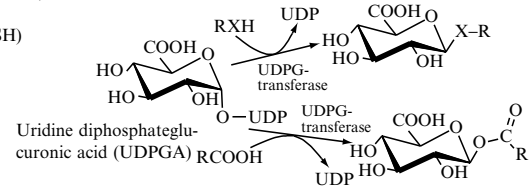
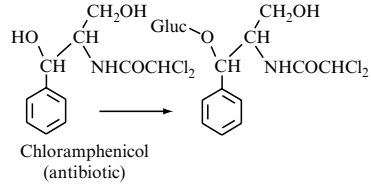
Phase II reactions, which are also known as **conjugation reactions**, may occur at any point in the metabolism of a drug or xenobiotic. However, they often represent the final step in the metabolic pathway before excretion. The products of Phase II reactions, which are referred to as **conjugates**, are usually pharmacologically inactive, although there are some notable exceptions. They are usually excreted in the urine and/or bile.

The reactions commonly involved in Phase II conjugation are acylation, sulphate formation and conjugation with amino acids, glucuronic acid, glutathione and mercapturic acid (Table 9.3). Methylation is also regarded as a Phase II reaction although it is normally a minor metabolic route. However, it can be a major route for phenolic hydroxy groups. In all cases, the reaction is usually catalysed by a specific transferase.

9.6 Pharmacokinetics of metabolites

The activity and behaviour of a metabolite will have a direct bearing on the safe use and dose of a drug administered to a patient. Consequently, when investigating the pharmacokinetics of a drug it is also necessary to obtain pharmacokinetic data concerning the action and elimination of its metabolites. This information is usually obtained in humans by administering the drug and measuring the change in concentration of the appropriate metabolite with time in the plasma. However, as metabolites are produced in the appropriate body compartment, a metabolite may be partly or fully metabolized before it reaches the plasma. In these cases the amount of metabolite found by analysis of plasma samples is only a fraction of the amount of the metabolite produced by the body. For simplicity, the discussions in this text assume that **all** the

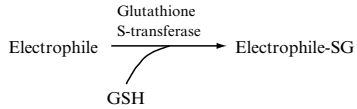
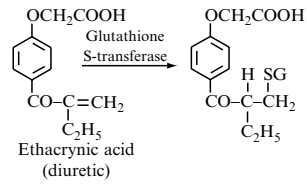
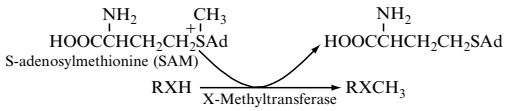
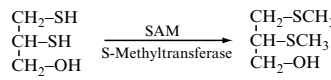
Table 9.3 Phase II reactions. These normally produce pharmacologically inert metabolites but a few metabolites, such as N-acetylisoniazid and the sulphate conjugates of phenacetin, are toxic

Phase II reaction. Functional group/notes	General reaction	Example
Acylation Primary aromatic amines ($ArNH_2$), Simple sulphonamides ($-SO_2NH_2$), Hydrazines ($-NHNH_2$), Hydrazides ($-CONHNH_2$), Phenols (ArOH).		
Sulphate formation Phenols (ArOH), Alcohols (ROH), Simple sulphonamides ($-SO_2NH_2$), Primary aromatic amines ($ArNH_2$.),	 3'-Phosphoadenosine-5'-phosphosulphate (PAPS) 3'-Phosphoadenosine -5'-phosphate (PAP)	
Conjugation with amino acids Acrboxylic acids (–COOH) The main amino acids used to form the conjugates are glycine, glutamine, ornithine (birds), alanine (hamsters and mice), arginine and taurine.		
Conjugation with glucuronic acid (Gluc) Carboxylic acids (RCOOH), Phenols (ArOH), Alcohols (ROH), Amines, Thiols (RSH)		

KEY:
UDP = Uridine diphosphate

(*continues overleaf*)

Table 9.3 (*continued*)

Phase II reaction. Functional group/notes	General reaction	Example
Conjugation with glutathione (GSH) Electrophilic centres caused by Halides, Nitro groups, Epoxides, Sulphonates, Organophosphate groups.		
Methylation Phenols (ArOH), Alcohols (ROH), Amines, N-heterocyclics. Methylation detoxifies a drug but produces a less polar and so less easily excreted metabolite.	 Dimercaprol (Heavy metal poisoning antidote)	

metabolite produced reaches the plasma. Alternatively, the metabolite may be administered separately when independent data concerning its activity and pharmacokinetics is required. However, observations made from metabolite administration can be suspect because its bioavailability is usually different to that when it is produced *in situ* from the drug.

The total administered dose (A) of a drug is excreted partly unchanged and partly metabolized (Figure 9.2). Most metabolic pathways consist of a series of steps. The importance of this series is not the number of steps but whether the pathway has a rate determining step. In other words, is there a metabolite bottleneck where the rate of elimination of a metabolite is far slower than its rate of formation from the drug? At such a point the concentration of the metabolite would increase to significant amounts, which could lead to potential clinical problems if the metabolite were pharmaceutically active. Consequently, to avoid problems of this nature a metabolite should be eliminated faster than

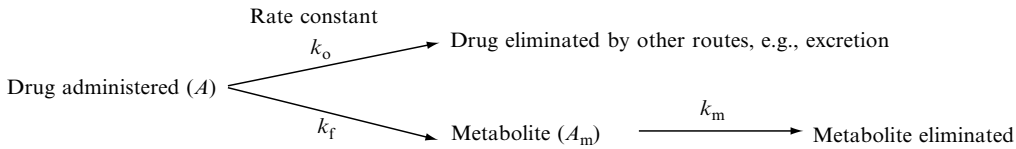


Figure 9.2 A schematic representation of the possible elimination routes for a drug in the body

the drug. The rate of change of concentration of a metabolite (dM/dt) in the plasma is given by:

$$dM/dt = \text{rate of formation} - \text{rate of elimination} \tag{9.1}$$

Since most biological processes exhibit first order kinetics Equation (9.1) becomes:

$$dM/dt = k_f A - k_m A_m \tag{9.2}$$

where k_f and k_m are the rate constants for the metabolite's formation and elimination processes respectively. If $k_f > k_m$ there will be an accumulation of the metabolite in the patient. However, it is not easy to determine k_f. Therefore, as all the processes involved in drug elimination are normally first order, the k overall rate constant for all the processes is used because $k = k_f + k_0$ and it is relatively easy to determine. Consequently, if $k > k_m$ the metabolite will be **likely** to accumulate in the plasma as it is formed faster than it is eliminated. However, if $k < k_m$ the metabolite is **unlikely** to accumulate in the body as the metabolite is eliminated faster than it is formed. The values of k and k_m can be determined experimentally from log plots of plasma measurements of the drug and metabolite (Figure 9.3).

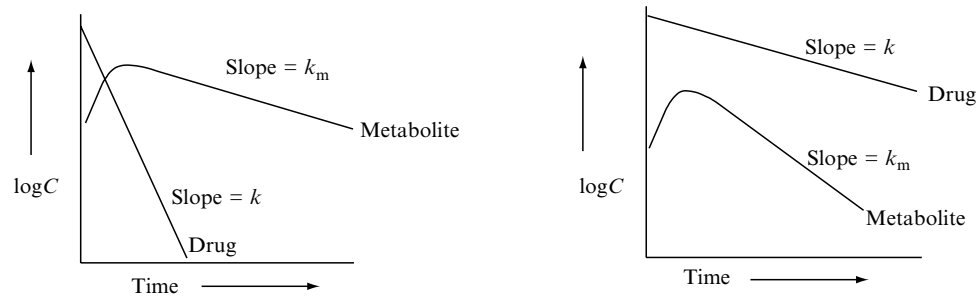


Figure 9.3 Representations of typical log concentration–time plots for a drug and metabolite exhibiting first order kinetics showing the general changes when (a) $k > k_m$ and (b) $k < k_m$

9.7 Drug metabolism and drug design

A knowledge of the metabolic pathway of a drug may be used to design analogues that have a different metabolism to that of the lead. This change of

metabolism is achieved by modifying the structure of the drug. These structural modifications may either make the analogue more stable or increase its ease of metabolism relative to the lead (see Table 9.4). The structural modifications should be selected so that they do not change the nature of the pharmacological activity of the drug. However, it is not possible to accurately predict whether this will be the case and so normally the activity of the analogue may only be found by experiment.

Changing the metabolism of a lead may result in an analogue which exhibits a different type of activity to that of the lead. For example, the replacement of the ester group in the local anaesthetic procaine by an amide group produced procainamide, which acts as an antiarrhythmic (Figure 9.4(a)). It may also be used to develop analogues that do not have undesireable side effects. For example, the local anaesthetic lignocaine is also used as an antiarrhythmic. In this respect, its undesirable convulsant and emetic side effects are caused by its metabolism in the liver by dealkylation to the mono-N-ethyl derivative (Figure 9.4(b)). The removal of the N-ethyl substituents and their replacement by an α-methyl group gives the antiarrhythmic tocainide. Tocainide cannot be metabolized by the same pathway as lignocaine and does not exhibit convulsant and emetic side effects.

Table 9.4 Examples of the effect of structural modifications on the metabolism of a lead compound

Change	Structural modification
Increased metabolic stability	Replace a reactive group by a less reactive group. For example, N-dealkylation can be prevented by replacing a N-methyl group by a N-t-butyl group. Reactive ester groups are replaced by less reactive amide groups. Oxidation of aromatic rings may be reduced by introducing strong electron acceptor substituents such as chloro (–Cl), quaternary amine ($-\overset{+}{N}R_3$), carboxylic acid (–COOH), sulphonate ($-SO_3R$) and sulphonamide ($-SO_2NHR$) groups.
Decreasing metabolic stability	The ease of metabolism of a drug may be increased by incorporating a metabolically labile group, such as an ester, in the structure of the drug. This type of approach is the basis of prodrug design (see section 9.8). It has also led to the development of so called *soft drugs*. These are biologically active compounds that are rapidly metabolized by a predictable route to pharmacologically nontoxic compounds. The advantage of this type of drug is that its half-life is so short that the possibility of the patient receiving a fatal overdose is considerably reduced.

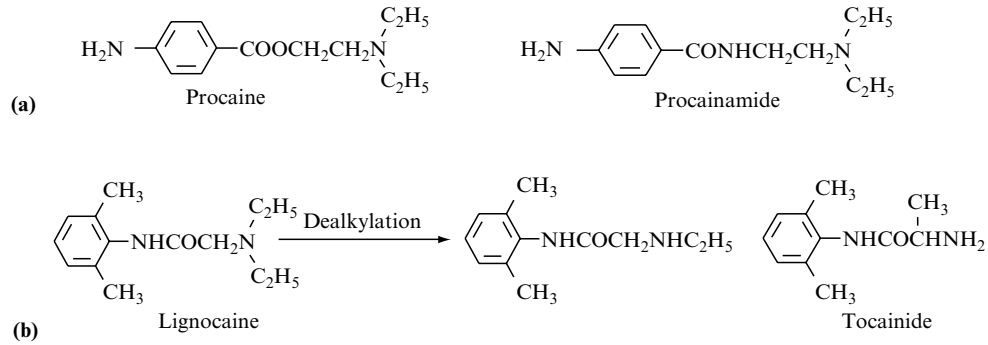


Figure 9.4 Examples of structural modifications causing changes in activity

9.8 Prodrugs

Prodrugs are compounds that are biologically inactive but are metabolized to an active metabolite, which is responsible for the drug's action. They are classified as either **bioprecursor** or **carrier prodrugs**. Prodrugs may be designed to improve absorption, improve patient acceptance, reduce toxicity and also for the slow release of drugs in the body. A number of prodrugs have also been designed to be site specific (see section 9.8.3).

9.8.1 Bioprecursor prodrugs

Bioprecursor prodrugs are compounds that already contain the embryo of the active species within their structure. This active species is liberated by metabolism of the prodrug (Figure 9.5).

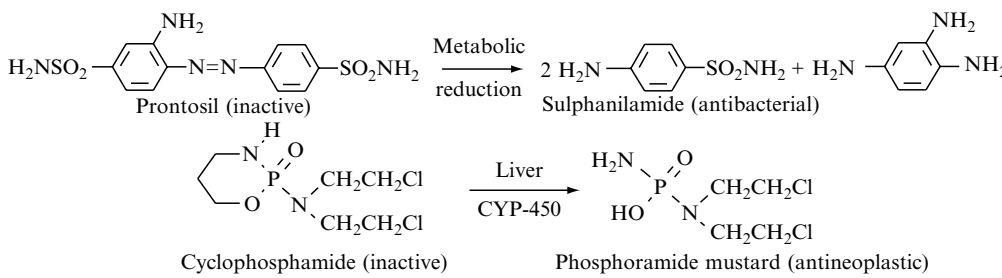


Figure 9.5 Examples of bioprecursor prodrugs